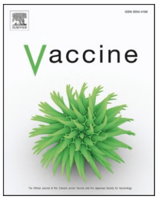
Vaccine 42 (2024) 2200–2211

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals

K. Faksova[a,*], D. Walsh[b,c], Y. Jiang[b,c], J. Griffin[c], A. Phillips[d], A. Gentile[e], J.C. Kwong[f,g,h], K. Macartney[d,i], M. Naus[j,n], Z. Grange[k], S. Escolano[l], G. Sepulveda[m], A. Shetty[m], A. Pillsbury[d], C. Sullivan[k], Z. Naveed[j,n], N.Z. Janjua[j,n], N. Giglio[e], J. Perälä[o], S. Nasreen[f,p,x], H. Gidding[d,i], P. Hovi[q], T. Vo[r], F. Cui[s], L. Deng[d], L. Cullen[k], M. Artama[r], H. Lu[b,c], H.J. Clothier[c,m], K. Batty[t], J. Paynter[u], H. Petousis-Harris[c,u], J. Buttery[c,m,v], S. Black[c,u], A. Hviid[a,w]

[a] Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
[b] Department of Statistics, University of Auckland, New Zealand
[c] Global Vaccine Data Network, Global Coordinating Centre, Auckland, New Zealand
[d] National Centre for Immunisation Research and Surveillance, Westmead, New South Wales, Australia
[e] Department of Epidemiology, Ricardo Gutierrez Children Hospital, Buenos Aires University, Argentina
[f] ICES, Toronto, Ontario, Canada
[g] Public Health Ontario, Toronto, Ontario, Canada
[h] Department of Family and Community Medicine, Temerty Faculty of Medicine and the Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[i] The University of Sydney, Australia
[j] British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada
[k] Public Health Scotland, Glasgow, Scotland, United Kingdom
[l] Université Paris-Saclay, UVSQ, Inserm, CESP, High Dimensional Biostatistics for Drug Safety and Genomics, Villejuif, France
[m] Murdoch Children's Research Institute, Parkville, Victoria, Australia
[n] School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada
[o] Department of Health Security, Finnish Institute for Health and Welfare, Helsinki, Finland
[p] Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[q] Department of Public Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland
[r] Faculty of Social Sciences, Tampere University, Finland
[s] School of Public Health, Peking University, China
[t] Auckland UniServices Limited at University of Auckland, New Zealand
[u] School of Population Health, University of Auckland, New Zealand
[v] University of Melbourne, Parkville, Victoria, Australia
[w] Pharmacovigilance Research Center, Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[x] School of Public Health, SUNY Downstate Health Sciences University, Brooklyn, NY, USA

ARTICLE INFO

Keywords:
Vaccine safety surveillance
Pharmacovigilance
Adverse events following immunization
Adverse events of special interest
COVID-19
Observed vs. expected analysis

ABSTRACT

Background: The Global COVID Vaccine Safety (GCoVS) Project, established in 2021 under the multinational Global Vaccine Data Network™ (GVDN®), facilitates comprehensive assessment of vaccine safety. This study aimed to evaluate the risk of adverse events of special interest (AESI) following COVID-19 vaccination from 10 sites across eight countries.

Methods: Using a common protocol, this observational cohort study compared observed with expected rates of 13 selected AESI across neurological, haematological, and cardiac outcomes. Expected rates were obtained by participating sites using pre-COVID-19 vaccination healthcare data stratified by age and sex. Observed rates were reported from the same healthcare datasets since COVID-19 vaccination program rollout. AESI occurring up to 42 days following vaccination with mRNA (BNT162b2 and mRNA-1273) and adenovirus-vector (ChAdOx1)

---

[*] Corresponding author at: Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, Copenhagen S 2300, Denmark.
E-mail address: kfak@ssi.dk (K. Faksova).

https://doi.org/10.1016/j.vaccine.2024.01.100
Received 29 January 2024; Accepted 30 January 2024
Available online 12 February 2024
0264-410X/© 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

vaccines were included in the primary analysis. Risks were assessed using observed versus expected (OE) ratios with 95 % confidence intervals. Prioritised potential safety signals were those with lower bound of the 95 % confidence interval (LBCI) greater than 1.5.

Results: Participants included 99,068,901 vaccinated individuals. In total, 183,559,462 doses of BNT162b2, 36,178,442 doses of mRNA-1273, and 23,093,399 doses of ChAdOx1 were administered across participating sites in the study period. Risk periods following homologous vaccination schedules contributed 23,168,335 person-years of follow-up. OE ratios with LBCI > 1.5 were observed for Guillain-Barré syndrome (2.49, 95 % CI: 2.15, 2.87) and cerebral venous sinus thrombosis (3.23, 95 % CI: 2.51, 4.09) following the first dose of ChAdOx1 vaccine. Acute disseminated encephalomyelitis showed an OE ratio of 3.78 (95 % CI: 1.52, 7.78) following the first dose of mRNA-1273 vaccine. The OE ratios for myocarditis and pericarditis following BNT162b2, mRNA-1273, and ChAdOx1 were significantly increased with LBCIs > 1.5.

Conclusion: This multi-country analysis confirmed pre-established safety signals for myocarditis, pericarditis, Guillain-Barré syndrome, and cerebral venous sinus thrombosis. Other potential safety signals that require further investigation were identified.

1. Introduction

Since declaration of the COVID-19 pandemic by the World Health Organization (WHO) on March 11, 2020 [1] more than 13.5 billion doses of COVID-19 vaccines have been administered worldwide [2]. As of November 2023, at least 70.5 % of the world's population had received at least one dose of a COVID-19 vaccine [2]. This unparalleled scenario underscores the pressing need for comprehensive vaccine safety monitoring as very rare adverse events associated with COVID-19 vaccines may only come to light after administration to millions of individuals.

In anticipation of this unprecedented global rollout of COVID-19 vaccines, the Safety Platform for Emergency vACcines (SPEAC) initiative formulated a list of potential COVID-19 vaccine adverse events of special interest (AESI) in 2020 [3]. AESI selection was based on their pre-established associations with immunization, specific vaccine platforms or adjuvants, or viral replication during wild-type disease; theoretical concerns related to immunopathogenesis; or supporting evidence from animal models using candidate vaccine platforms [3].

One flexible approach for assessing AESI is the comparison of observed AESI rates following the introduction of a vaccine program with the expected (or background) rates based on historical periods pre-vaccine roll out [4,5]. Such comparisons can be executed rapidly and can play a key role in early detection of potential vaccine safety signals or when regulatory and public health agencies need rapid assessment of an emerging safety signal [4,6]. Observed versus (vs.) expected (OE) analysis was integral in identifying thrombosis with thrombocytopenia syndrome (TTS) as a safety signal, prompting the suspension of use of the ChAdOx1 (AstraZeneca COVID-19 vaccine) on March 11, 2021, in Denmark and Norway [7,8].

These evaluations are not only valuable early-on in large-scale vaccine deployment, but also as the vaccination program matures, especially if they can be conducted in a multi-country context. We conducted a global cohort study following the Observed vs. Expected Analyses of COVID-19 Adverse Events of Special Interest Study Protocol [9] with data from 10 sites across eight countries participating in the unique Global COVID Vaccine Safety (GCoVS) Project [10] of the Global Vaccine Data Network™ (GVDN®) [11]. The GCoVS Project, initiated in 2021, is a Centers for Disease Control and Prevention (CDC) funded global collaboration of investigators and data sources from multiple nations for the purpose of COVID-19 vaccine safety monitoring.

2. Methods

2.1. Study design

This retrospective observational study was designed to estimate the OE ratios of selected AESIs after COVID-19 vaccination in a multi-country population cohort.

2.2. Data source and study population

The GCoVS Project compiled electronic healthcare data on AESI related to COVID-19 vaccines from participants across multiple sites within the GVDN network, including Argentina, Australia – New South Wales, Australia – Victoria, Canada – British Columbia, Canada – Ontario, Denmark, Finland, France, New Zealand, and Scotland [10]. The healthcare data comprised of either individual- or population-level data, depending on the availability in the study sites (Supplementary Table 1).

Immunization registers containing individual-level vaccination data were utilized by the majority of study sites. These registers covered the same population and geographic region as the data sets used to calculate background rates. We also examined population-level data on vaccination uptake using regularly updated dashboards from the study sites. If the number of individuals vaccinated in specific age and gender groups was available, we converted those numbers into person-years based on the post-vaccination risk period. Unlike the registers with individual-level data, the age and sex strata used in this approach might not have matched the strata used in the background rates calculations.

Participants were individuals vaccinated with COVID-19 vaccines in the populations represented by the sites. To the extent possible, standardized methods were applied across sites. Patient types included hospital inpatients (Australia – New South Wales, France, New Zealand, Scotland), and combinations of inpatient and outpatient emergency department patients (Argentina, Australia – Victoria, Canada, Denmark, Finland). In countries without clearly defined patient types, hospital contact duration was used as a proxy for patient types. As an example, a contact duration of five hours or longer was used as a proxy for inpatients in Denmark. Site-specific characteristics of data sources and data are presented in Supplementary Table 1.

2.3. Study period and follow-up

The study periods varied across countries, commencing on the date of the site-specific COVID-19 vaccination program rollout, and concluding at the end of data availability (Table 1). In general, the study periods spanned from December 2020 until August 2023. The shortest study period observed occurred in Australia – New South Wales, including 11 months from February 2021 to December 2021. Argentina had the longest study period, from December 2020 to August 2023, encompassing a total of 32 months.

The risk intervals used after each dose were 0–7 days, 8–21 days, 22–42 days, and 0–42 days. For each vaccination dose, day 0 was denoted the day of vaccine receipt. For this manuscript, we present results for the risk interval of 0–42 days only. More data are presented on the GVDN dashboard with all latest updates from participating sites [12]. Outcome events that occurred outside the study period were not included. A 365-day washout period for outcome events was used to define incident outcomes. Outcome events were considered incident if there was no record of the same outcome event during the preceding 365-day washout period. An individual may have contributed several outcome events on the condition they were separated in time by at least the washout period of 365 days.

2.4. *Study variables and outcomes*

2.4.1. *Adverse events of special interest (AESI)*

Thirteen conditions representing AESI of specific relevance to the current landscape of real-world vaccine pharmacovigilance were selected from the list compiled by the Brighton Collaboration SPEAC Project [3] and in response to the safety signals of thrombosis with thrombocytopenia syndrome [7,8] (Supplementary Table 2). The conditions chosen matched the AESI for which background rates were recently generated by GVDN sites [13]. AESI were identified using harmonized International Classification of Diseases 10th Revision (ICD-10) codes. Neurological conditions selected included Guillain-Barré syndrome (GBS), transverse myelitis (TM), facial (Bell's) palsy, acute disseminated encephalomyelitis (ADEM), and convulsions (generalized seizures (GS) and febrile seizures (FS)) as potential safety signals have been identified for some of these conditions [14–16]. Hematologic conditions included cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis (SVT) and pulmonary embolism (PE); the unusual site thromboses (CVST and SVT) were selected as markers of potential TTS that could be accurately identified using diagnostic codes [17,18]. Thrombocytopenia and immune thrombocytopenia (ITP) were also included due to their association with TTS and reports of ITP as an independent safety signal [7,19,20]. Myocarditis and pericarditis were included as cardiovascular conditions and the OE ratios were evaluated separately for each condition [21–23].

2.4.2. *COVID-19 vaccines*

As of November 2023, multiple vaccines against COVID-19 were in use by the GCoVS sites representing multiple platform types such as inactivated, nucleic acid-based (mRNA), protein-based, and non-replicating viral vector platforms (Table 2). For this manuscript, we focused on three vaccines that recorded the highest number of doses administered, Pfizer/BioNTech BNT162b2, Moderna mRNA-1273, and Oxford/Astra Zeneca/Serum Institute of India ChAdOx1 vaccines. The cumulative number of doses of other vaccines administered (n) across study sites were relatively low, with exceptions for the inactivated Sinopharm (n = 134,550) and Sinovac (n = 31,598) vaccines, the protein-based Novavax (n = 66,856) vaccine, and the adenovirus-vector Janssen/Johnson & Johnson (n = 1,137,505) and Gamaleya Research Institute/Sputnik (n = 84,460) vaccines. The total number of doses of each vaccine brand administered are outlined in Table 2. Exposure to COVID-19 vaccine by platform/type, brand, and dose data were available at the individual level to determine the number of observed cases by vaccine type/brand and dose profile and within the 0–42 days post-vaccination risk interval.

Table 2
Total number of vaccinations by brand.

Vaccine platform	Vaccine brand	Total doses
Inactivated	Covilo or SARS-CoV-2 Vaccine (Vero Cell) [Sinopharm (Beijing)]	134,550
	Covaxin [Bharat Biotech]	1,660
	CoronaVac or Sinovac [Sinovac Biotech]	31,598
	Inactivated (Vero cell) [Sinopharm (Wuhan)]	623
Nucleic acid-based	Comirnaty or Riltozinameran or Pfizer/BioNTech COVID-19 Vaccine Bivalent [Pfizer/BioNTech]	3,516,963
	Comirnaty or Tozinameran [Pfizer/BioNTech or Fosun-BioNTech]	183,677,660
	Comirnaty or Tozinameran Paediatric [Pfizer/BioNTech or Fosun-BioNTech]	2,439,086
	Spikevax bivalent Original/Omicron [Moderna]	2,750,476
	Elasomeran or Spikevax or TAK-919 Half Dose [Moderna or Takeda]	400,395
	Elasomeran or Spikevax or TAK-919 [Moderna or Takeda]	36,222,514
Protein-based	MVC-COV1901 [Medigen]	16
	Covovax or Nuvaxoid [Novavax or Serum Institute of India]	66,856
Non-replicating viral vector	Convidecia or Convidence [CanSino]	3,938
	Covishield or Vaxzevria [AstraZeneca or Serum Institute of India]	23,094,620
	Sputnik Light or Gam-COVID-Vac [Gamaleya Research Institute]	26
	Sputnik V [Gamaleya Research Institute]	84,460
	Janssen [Janssen/Johnson & Johnson]	1,137,505

2.5. *Statistical analysis*

2.5.1. *Calculation of observed vs. expected ratios for each site*

For each site, we calculated the observed number of events for each AESI in the risk interval after introduction of COVID-19 vaccination. To

Table 1
Population summary by site. (Only Pfizer/BioNTech BNT162b2, Moderna mRNA-1273, and Oxford/Astra Zeneca/Serum Institute of India ChAdOx1 vaccines and doses 1–4 included).

Characteristics		Argentina	Australia: NSW	Australia: Victoria	Canada: BC	Canada: Ontario	Denmark	Finland	France	New Zealand	Scotland
Study period		12/2020-08/2023	02/2021-12/2021	02/2021-06/2023	12/2020-05/2023	12/2020-03/2023	12/2020-02/2023	12/2020-06/2022	01/2021-12/2021	02/2021-09/2022	12/2020-05/2023
Vaccinated population	n	157,883	6,492,805	5,789,070	4,267,644	12,081,337	4,291,034	4,501,659	52,795,394	4,151,269	4,540,806
	Female (%)	78,374 (49.6)	3,289,381 (50.7)	2,925,886 (50.5)	2,183,666 (51.2)	6,192,991 (51.3)	2,179,415 (50.8)	2,324,067 (51.6)	27,216,365 (51.6)	2,100,071 (50.6)	2,346,694 (51.7)
	0-19 (%)	42,281 (26.8)	692,498 (10.7)	921,635 (15.9)	274,813 (6.4)	1,882,574 (15.6)	620,273 (14.5)	549,589 (12.2)	5,585,455 (10.6)	582,662 (14.0)	501,397 (11.0)
	20-39 (%)	58,567 (37.1)	2,125,624 (32.7)	1,858,706 (32.1)	1,386,513 (32.5)	3,421,403 (28.3)	1,100,566 (25.6)	1,159,303 (25.8)	14,517,426 (27.5)	1,321,332 (31.8)	1,218,142 (26.8)
	40-59 (%)	40,484 (25.6)	1,933,770 (29.8)	1,586,558 (27.4)	1,244,817 (29.2)	3,460,295 (28.6)	1,263,265 (29.4)	1,256,439 (27.9)	16,065,061 (30.4)	1,198,750 (28.9)	1,418,313 (31.2)
	60-79 (%)	15,167 (9.6)	1,433,446 (22.1)	1,139,623 (19.7)	1,103,315 (25.9)	2,706,343 (22.4)	1,063,018 (24.8)	1,234,825 (27.4)	12,997,416 (24.6)	865,928 (20.9)	1,142,053 (25.2)
	80+ (%)	1,384 (0.9)	307,467 (4.7)	282,548 (4.9)	258,186 (6.0)	610,722 (5.1)	243,912 (5.7)	301,503 (6.7)	3,630,036 (6.9)	182,597 (4.4)	260,901 (5.7)
BNT162b2	Dose 1		3,896,923 (60.0)	3,393,207 (58.6)	2,959,369 (69.3)	8,473,103 (70.1)	3,425,161 (79.8)	3,586,237 (79.7)	41,450,092 (78.5)	4,036,859 (97.2)	2,087,109 (46.0)
	Dose 2		3,837,153 (59.1)	3,313,758 (57.2)	2,778,036 (65.1)	7,382,893 (61.1)	3,480,685 (81.1)	3,594,661 (79.9)	38,876,671 (73.6)	3,990,353 (96.1)	1,967,726 (43.3)
	Dose 3		751,169 (11.6)	2,900,036 (50.1)	1,295,609 (30.4)	4,377,649 (36.2)	2,811,507 (65.5)	2,167,380 (48.1)	16,121,693 (30.5)	2,730,880 (65.8)	2,557,434 (56.3)
	Dose 4			969,442 (16.7)	259,228 (6.1)	1,469,297 (12.2)	1,609,558 (37.5)		54,905 (0.1)	595,269 (14.3)	358,410 (7.9)
mRNA-1273	Dose 1	2,850 (1.8)	134,960 (2.1)	199,865 (3.5)	940,656 (22.0)	2,100,866 (17.4)	507,031 (11.8)	554,076 (12.3)	5,853,595 (11.1)	3,255 (0.1)	205,528 (4.5)
	Dose 2	13,046 (8.3)	126,291 (1.9)	190,271 (3.3)	1,196,017 (28.0)	3,589,447 (29.7)	578,985 (13.5)	532,153 (11.8)	5,880,520 (11.1)	3,211 (0.1)	183,966 (4.1)
	Dose 3	45,712 (29.0)	117,804 (1.8)	617,724 (10.7)	1,482,817 (34.7)	2,965,640 (24.5)	61,548 (1.4)	812,002 (18.0)	4,676,771 (8.9)	2,184 (0.1)	970,917 (21.4)
	Dose 4			257,557 (4.4)	380,862 (8.9)	723,201 (6.0)	56,850 (1.3)		14,245 (<0.1)	134 (<0.1)	195,885 (4.3)
ChAdOx1	Dose 1	37,721 (23.9)	2,460,922 (37.9)	1,868,764 (32.3)	308,867 (7.2)	856,603 (7.1)	133,181 (3.1)	360,196 (8.0)	4,398,411 (8.3)	17,087 (0.4)	2,139,669 (47.1)
	Dose 2	36,164 (22.9)	2,433,046 (37.5)	1,835,469 (31.7)	132,111 (3.1)	221,118 (1.8)	1,780 (<0.1)	191,120 (4.2)	3,424,058 (6.5)	14,560 (0.4)	2,093,121 (46.1)
	Dose 3	28,255 (17.9)	7,483 (0.1)	57,841 (1)	1,757 (<0.1)		46 (<0.1)	306 (<0.1)	7,368 (<0.1)	2,058 (<0.1)	9,551 (0.2)
	Dose 4			13,693 (0.2)	76 (<0.1)				90 (<0.1)	212 (<0.1)	695 (<0.1)

Vaccines: Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1).

calculate the expected number of cases, we used pre-COVID-19 vaccination background rates data from 2015 to 2019 (2019–2020 for Denmark) collected in the GCoVS Background Rates of AESI Following COVID-19 vaccination study [13]. The observed follow-up period in person-years for a given vaccination profile and post-vaccination period was stratified according to age group and sex. Each of the age-sex stratified person-years were multiplied by the corresponding age-sex stratified background rate. This resulted in the expected number of cases in each stratum, which were then summed to give the total number of expected cases during the observed follow-up period.

The aggregated OE ratios by last dose were calculated by dividing the observed number of cases by the expected number of cases in the post-vaccination period, 95 % confidence intervals (CI) were derived using the exact Poisson distribution. We also calculated OE ratios for homologous schedules for BNT162b2, mRNA-1273, and ChAdOx1 vaccines up to four doses. Both the aggregated OE ratios and those specific to homologous schedules are presented.

We considered an OE ratio a potential safety signal of concern where the lower bound of the 95 % CI (LBCI) was greater than one and reached statistical significance [5]. However, we prioritised potential safety signals of concern for further evaluation where the LBCI was greater than 1.5, due to increased statistical evidence and the higher likelihood of being a true signal, based on expert opinion from the CDC and GVDN collaborators.

2.5.2. *Combining results across sites*

The results were aggregated across sites by summing the observed number of events for each AESI and the age-sex stratified person-years for a given vaccination profile and post-vaccination period. For each AESI, individual vaccine profiles were reported if the cumulative amount of follow up (in person-years) in the 0–42 days post-vaccination period was 10,000 or greater. The combined numbers of events and the OE ratio was calculated with 95 % CIs derived using the exact Poisson distribution. No event (i.e., zero) observed for a vaccine brand and dose profile was reported separately without CI.

2.5.3. *Sensitivity analysis*

Firstly, we conducted site-specific sensitivity analyses to further explore potential associations of the most significant safety signals identified in the main analysis. The observed rates reported by sites were considered in the analysis based on the following constraints. For each vaccine brand and dose profile, and post-vaccination period combination, the OE ratios and 95 % CI were suppressed if fewer than five events were observed. Secondly, we conducted supplemental analysis including other vaccines and doses administered across sites. The person-years threshold for reporting was lowered from 10,000 to 1,000 person-years compared to the main aggregated OE ratios analysis, allowing for broader scope of vaccines to be analysed.

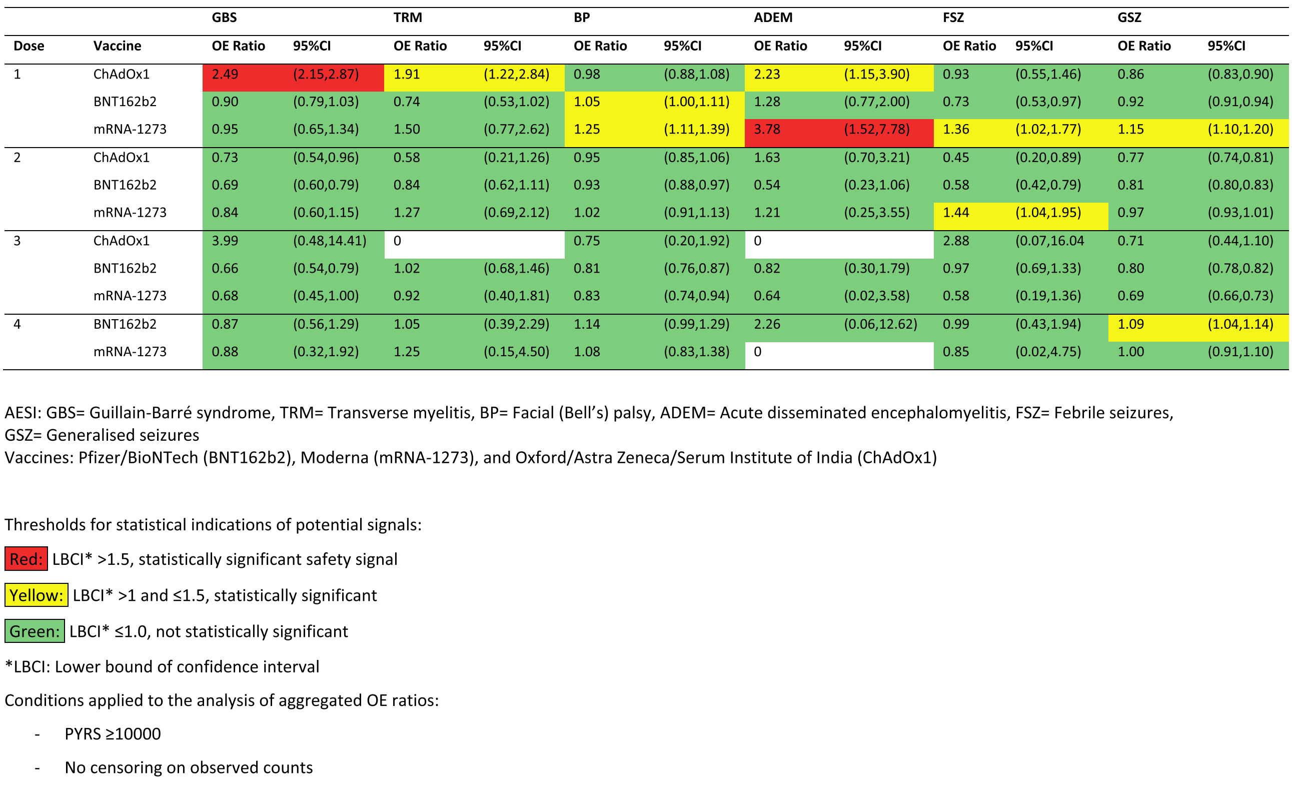
2.6. *Ethical approval*

Approval from the relevant Human Research Ethics Committees was either acquired or an exemption obtained for all participating sites (Supplementary Table 3).

3. Results

The total vaccinated population across all sites comprised 99,068,901 individuals. Most vaccine recipients were in the 20–39 and 40–59-year age groups (Table 1). In total, 183,559,462 doses of BNT162b2, 36,178,442 doses of mRNA-1273, and 23,093,399 doses of ChAdOx1 were administered across all the sites in the study periods. The

Table 3
Aggregated OE Ratios by last dose, neurological conditions, period 0–42 days.



		GBS		TRM		BP		ADEM		FSZ		GSZ	
Dose	**Vaccine**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**
1	ChAdOx1	2.49	(2.15,2.87)	1.91	(1.22,2.84)	0.98	(0.88,1.08)	2.23	(1.15,3.90)	0.93	(0.55,1.46)	0.86	(0.83,0.90)
	BNT162b2	0.90	(0.79,1.03)	0.74	(0.53,1.02)	1.05	(1.00,1.11)	1.28	(0.77,2.00)	0.73	(0.53,0.97)	0.92	(0.91,0.94)
	mRNA-1273	0.95	(0.65,1.34)	1.50	(0.77,2.62)	1.25	(1.11,1.39)	3.78	(1.52,7.78)	1.36	(1.02,1.77)	1.15	(1.10,1.20)
2	ChAdOx1	0.73	(0.54,0.96)	0.58	(0.21,1.26)	0.95	(0.85,1.06)	1.63	(0.70,3.21)	0.45	(0.20,0.89)	0.77	(0.74,0.81)
	BNT162b2	0.69	(0.60,0.79)	0.84	(0.62,1.11)	0.93	(0.88,0.97)	0.54	(0.23,1.06)	0.58	(0.42,0.79)	0.81	(0.80,0.83)
	mRNA-1273	0.84	(0.60,1.15)	1.27	(0.69,2.12)	1.02	(0.91,1.13)	1.21	(0.25,3.55)	1.44	(1.04,1.95)	0.97	(0.93,1.01)
3	ChAdOx1	3.99	(0.48,14.41)	0		0.75	(0.20,1.92)	0		2.88	(0.07,16.04	0.71	(0.44,1.10)
	BNT162b2	0.66	(0.54,0.79)	1.02	(0.68,1.46)	0.81	(0.76,0.87)	0.82	(0.30,1.79)	0.97	(0.69,1.33)	0.80	(0.78,0.82)
	mRNA-1273	0.68	(0.45,1.00)	0.92	(0.40,1.81)	0.83	(0.74,0.94)	0.64	(0.02,3.58)	0.58	(0.19,1.36)	0.69	(0.66,0.73)
4	BNT162b2	0.87	(0.56,1.29)	1.05	(0.39,2.29)	1.14	(0.99,1.29)	2.26	(0.06,12.62)	0.99	(0.43,1.94)	1.09	(1.04,1.14)
	mRNA-1273	0.88	(0.32,1.92)	1.25	(0.15,4.50)	1.08	(0.83,1.38)	0		0.85	(0.02,4.75)	1.00	(0.91,1.10)

AESI: GBS= Guillain-Barré syndrome, TRM= Transverse myelitis, BP= Facial (Bell's) palsy, ADEM= Acute disseminated encephalomyelitis, FSZ= Febrile seizures, GSZ= Generalised seizures
Vaccines: Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1)

Thresholds for statistical indications of potential signals:

Red: LBCI* >1.5, statistically significant safety signal

Yellow: LBCI* >1 and ≤1.5, statistically significant

Green: LBCI* ≤1.0, not statistically significant

*LBCI: Lower bound of confidence interval

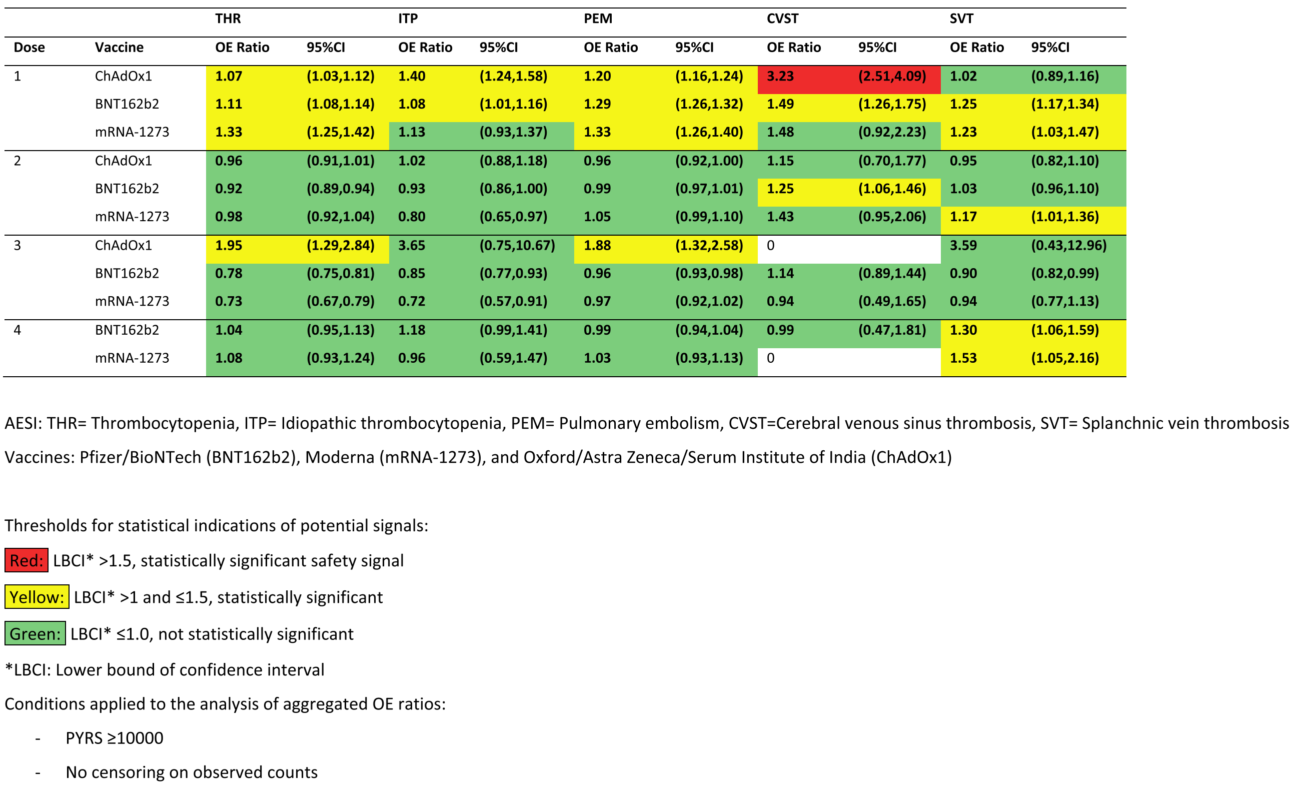
Conditions applied to the analysis of aggregated OE ratios:

- PYRS ≥10000
- No censoring on observed counts

AESI: GBS = Guillain-Barré syndrome, TRM = Transverse myelitis, BP = Facial (Bell's) palsy, ADEM = Acute disseminated encephalomyelitis, FSZ = Febrile seizures, GSZ = Generalised seizures.
Vaccines: Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1).

Table 4

Aggregated OE Ratios by last dose, haematologic conditions, period 0–42 days.



		THR		ITP		PEM		CVST		SVT	
Dose	**Vaccine**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**
1	ChAdOx1	**1.07**	**(1.03,1.12)**	**1.40**	**(1.24,1.58)**	**1.20**	**(1.16,1.24)**	**3.23**	**(2.51,4.09)**	**1.02**	**(0.89,1.16)**
	BNT162b2	**1.11**	**(1.08,1.14)**	**1.08**	**(1.01,1.16)**	**1.29**	**(1.26,1.32)**	**1.49**	**(1.26,1.75)**	**1.25**	**(1.17,1.34)**
	mRNA-1273	**1.33**	**(1.25,1.42)**	**1.13**	**(0.93,1.37)**	**1.33**	**(1.26,1.40)**	**1.48**	**(0.92,2.23)**	**1.23**	**(1.03,1.47)**
2	ChAdOx1	**0.96**	**(0.91,1.01)**	**1.02**	**(0.88,1.18)**	**0.96**	**(0.92,1.00)**	**1.15**	**(0.70,1.77)**	**0.95**	**(0.82,1.10)**
	BNT162b2	**0.92**	**(0.89,0.94)**	**0.93**	**(0.86,1.00)**	**0.99**	**(0.97,1.01)**	**1.25**	**(1.06,1.46)**	**1.03**	**(0.96,1.10)**
	mRNA-1273	**0.98**	**(0.92,1.04)**	**0.80**	**(0.65,0.97)**	**1.05**	**(0.99,1.10)**	**1.43**	**(0.95,2.06)**	**1.17**	**(1.01,1.36)**
3	ChAdOx1	**1.95**	**(1.29,2.84)**	**3.65**	**(0.75,10.67)**	**1.88**	**(1.32,2.58)**	0		**3.59**	**(0.43,12.96)**
	BNT162b2	**0.78**	**(0.75,0.81)**	**0.85**	**(0.77,0.93)**	**0.96**	**(0.93,0.98)**	**1.14**	**(0.89,1.44)**	**0.90**	**(0.82,0.99)**
	mRNA-1273	**0.73**	**(0.67,0.79)**	**0.72**	**(0.57,0.91)**	**0.97**	**(0.92,1.02)**	**0.94**	**(0.49,1.65)**	**0.94**	**(0.77,1.13)**
4	BNT162b2	**1.04**	**(0.95,1.13)**	**1.18**	**(0.99,1.41)**	**0.99**	**(0.94,1.04)**	**0.99**	**(0.47,1.81)**	**1.30**	**(1.06,1.59)**
	mRNA-1273	**1.08**	**(0.93,1.24)**	**0.96**	**(0.59,1.47)**	**1.03**	**(0.93,1.13)**	0		**1.53**	**(1.05,2.16)**

AESI: THR= Thrombocytopenia, ITP= Idiopathic thrombocytopenia, PEM= Pulmonary embolism, CVST=Cerebral venous sinus thrombosis, SVT= Splanchnic vein thrombosis

Vaccines: Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1)

Thresholds for statistical indications of potential signals:

Red: LBCI* >1.5, statistically significant safety signal

Yellow: LBCI* >1 and ≤1.5, statistically significant

Green: LBCI* ≤1.0, not statistically significant

*LBCI: Lower bound of confidence interval

Conditions applied to the analysis of aggregated OE ratios:

- PYRS ≥10000
- No censoring on observed counts

AESI: THR = Thrombocytopenia, ITP = Idiopathic thrombocytopenia, PEM = Pulmonary embolism, CVST = Cerebral venous sinus thrombosis, SVT = Splanchnic vein thrombosis.

Vaccines: Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1).

highest numbers of doses were administered in France (120,758,419), followed by Canada – Ontario (32,159,817) and Australia – Victoria (15,617,627). In total, 23,168,335 person-years contributed to the OE ratios for the AESI following homologous schedules. The population summary is presented in Table 1, and more detailed information on the other administered vaccines are presented in Supplementary Table 4. In the results sections below, we provide both aggregated OE ratios (Tables 3–5) and detailed OE ratios for homologous schedules (Figs. 1–3), including the number of events and person-years. Overall, 95.8 % and 86.6 % of vaccinations were included in the aggregated and the homologous schedules analysis, respectively (Supplementary Table 5). The primary results from the individual sites as well as additional risk periods and meta-analyses for each AESI are available in the interactive GVDN Observed vs Expected (OE) Dashboard [12].

3.1. Neurological conditions

There was a statistically significant increase in GBS cases within 42 days after a first ChAdOx1 dose (OE ratio = 2.49; 95 % CI: 2.15, 2.87), indicating a prioritised safety signal (Table 3). Seventy-six GBS events were expected, and 190 events were observed (Fig. 1). The OE ratio for ADEM within 42 days after a first mRNA-1273 dose also fulfilled the significance threshold of a prioritised safety signal (3.78; 95 % CI: 1.52, 7.78), with two expected events compared with seven observed events (Fig. 1).

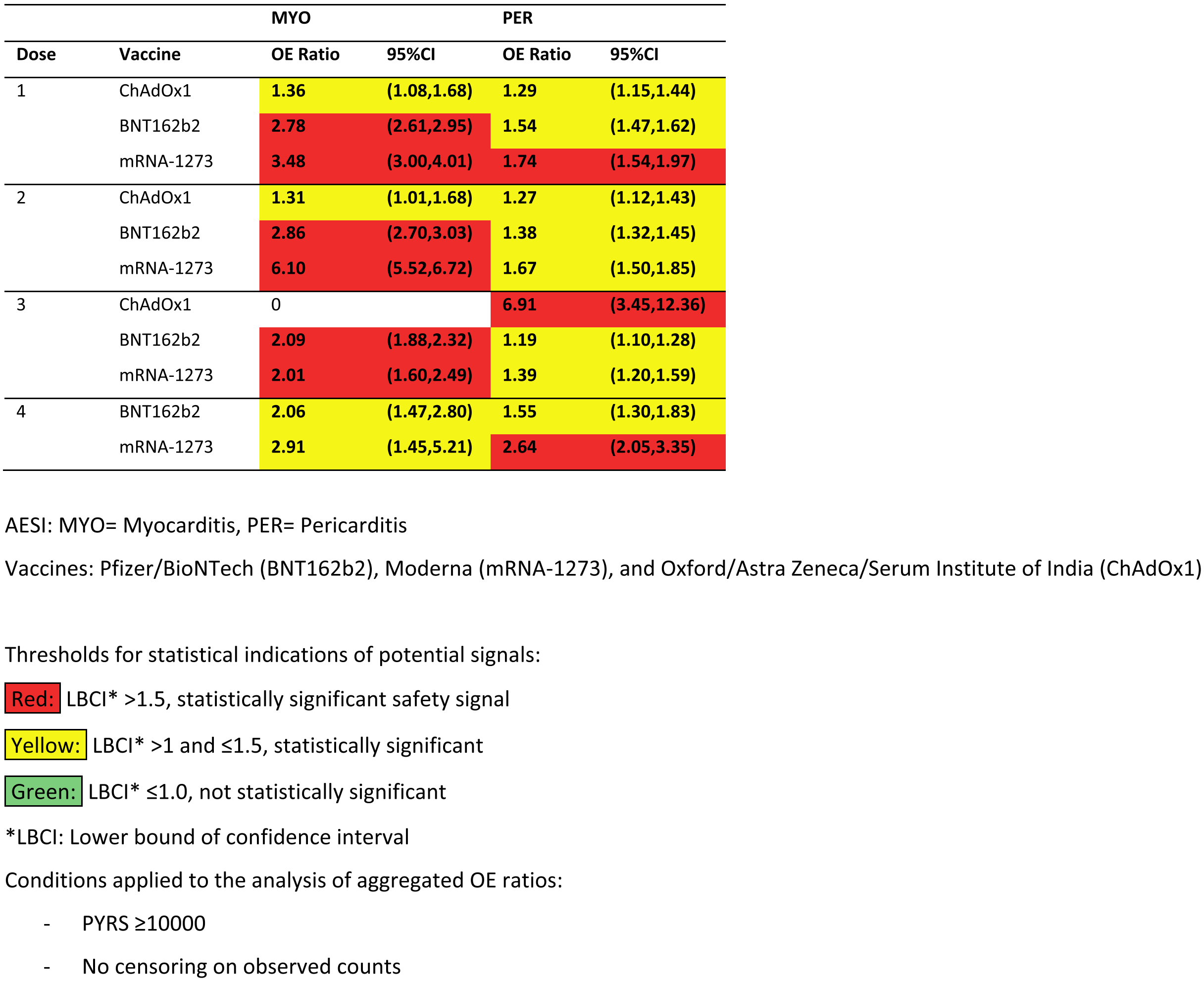
Statistically significant differences were also found for transverse myelitis (OE ratio = 1.91; 95 % CI: 1.22, 2.84) and ADEM (OE ratio = 2.23; 95 % CI: 1.15, 3.90) after a first ChAdOx1 dose. Bell's palsy had an increased OE ratio after a first dose of BNT162b2 (1.05; 95 % CI: 1.00, 1.11) and mRNA-1273 (1.25; 95 % CI: 1.11, 1.39). There were also increased OE ratios for febrile seizures following a first and second dose of mRNA-1273 (1.36, 95 % CI: 1.02, 1.77 and 1.44, 95 % CI: 1.04, 1.95, respectively), and for generalised seizures following a first mRNA-1273 dose (1.15, 95 % CI: 1.10, 1.20) and a fourth BNT162b2 dose (1.09, 95 % CI: 1.04, 1.14). No increased OE ratios were identified following a third dose of any vaccine. The results are concordant with the OE ratios of homologous schedules; however, an increased OE ratio for generalized seizures following a homologous schedule of four doses of mRNA-1273 (1.33; 95 % CI: 1.07, 1.63) was identified (Fig. 1). These outcomes did not meet the threshold for a prioritised safety signal following vaccination.

3.2. Hematologic conditions

The OE ratio of CVST was 3.23 (95 % CI: 2.51–4.09) within 42 days after a first dose of ChAdOx1, fulfilling the threshold of a prioritised safety signal (Table 4). In total, 21 events were expected, while 69 events were observed (Fig. 2).

Increased OE ratios were also identified for thrombocytopenia after a first dose of ChAdOx1 (1.07; 95 % CI: 1.03, 1.12), BNT162b2 (1.11; 95 % CI: 1.08, 1.14), and mRNA-1273 (1.33; 95 % CI 1.25, 1.42), as well as after a third dose of ChAdOx1 (1.95; 95 % CI: 1.29, 2.84). Immune thrombocytopenia also demonstrated increased OE ratios after a first dose of ChAdOx1 (1.40; 95 % CI: 1.24, 1.58) and BNT162b2 (1.08; 95 % CI: 1.01, 1.16). Pulmonary embolism OE ratios were increased following first doses of ChAdOx1 (1.20; 95 % CI: 1.16, 1.24), BNT162b2 (1.29; 95 % CI: 1.26, 1.32), and mRNA-1273 (1.33, 95 % CI: 1.26, 1.40), as well as after a third dose of ChAdOx1 (1.88; 95 % CI: 1.32, 2.58). The OE ratio of CVST was 1.49 (95 % CI: 1.26, 1.75) after a first dose and 1.25 (95 % CI: 1.06, 1.46) after a second dose of BNT162b2. An increased OE ratio for SVT was found after a first dose of BNT162b2 (1.25; 95 % CI: 1.17, 1.34) and mRNA-1273 (1.23; 95 % CI: 1.03, 1.47); a second dose of

Table 5
Aggregated OE Ratios by last dose, cardiovascular conditions, period 0–42 days.



		MYO		PER	
Dose	**Vaccine**	**OE Ratio**	**95%CI**	**OE Ratio**	**95%CI**
1	ChAdOx1	**1.36**	**(1.08,1.68)**	**1.29**	**(1.15,1.44)**
	BNT162b2	**2.78**	**(2.61,2.95)**	**1.54**	**(1.47,1.62)**
	mRNA-1273	**3.48**	**(3.00,4.01)**	**1.74**	**(1.54,1.97)**
2	ChAdOx1	**1.31**	**(1.01,1.68)**	**1.27**	**(1.12,1.43)**
	BNT162b2	**2.86**	**(2.70,3.03)**	**1.38**	**(1.32,1.45)**
	mRNA-1273	**6.10**	**(5.52,6.72)**	**1.67**	**(1.50,1.85)**
3	ChAdOx1	0		**6.91**	**(3.45,12.36)**
	BNT162b2	**2.09**	**(1.88,2.32)**	**1.19**	**(1.10,1.28)**
	mRNA-1273	**2.01**	**(1.60,2.49)**	**1.39**	**(1.20,1.59)**
4	BNT162b2	**2.06**	**(1.47,2.80)**	**1.55**	**(1.30,1.83)**
	mRNA-1273	**2.91**	**(1.45,5.21)**	**2.64**	**(2.05,3.35)**

AESI: MYO= Myocarditis, PER= Pericarditis

Vaccines: Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1)

Thresholds for statistical indications of potential signals:

Red: LBCI* >1.5, statistically significant safety signal

Yellow: LBCI* >1 and ≤1.5, statistically significant

Green: LBCI* ≤1.0, not statistically significant

*LBCI: Lower bound of confidence interval

Conditions applied to the analysis of aggregated OE ratios:

- PYRS ≥10000
- No censoring on observed counts

mRNA-1273 (1.17; 95 % CI: 1.01, 1.36); and a fourth dose of BNT162b2 (1.30, 95 % CI: 1.06, 1.59) and mRNA-1273 (1.53, 95 % CI: 1.05, 2.16). These outcomes did not meet the threshold for a prioritised safety signal following vaccination.

3.3. Cardiovascular conditions

Increased OE ratios fulfilling the threshold of prioritised safety signals for myocarditis were consistently identified following a first, second and third dose of mRNA vaccines (BNT162b2 and mRNA-1273) (Table 4). The highest OE ratio was observed following a first and second dose of mRNA-1273 (3.48; 95 % CI: 3.00, 4.01 and 6.10; 95 % CI: 5.52, 6.72, respectively). The OE ratio following a third dose of mRNA-1273 was 2.01 (95 % CI: 1.60, 2.49). The numbers of events for up to four doses of homologous schedules are shown in Fig. 3. The OE ratios of homologous schedules align with the aggregated OE ratios. The homologous OE for myocarditis following four doses of mRNA-1273 vaccine could not be estimated due to a lack of observed events.

Similarly, the OE ratio for pericarditis fulfilled the threshold of a prioritised safety signal following a first and fourth dose of mRNA-1273, with OE ratios of 1.74 (95 % CI: 1.54, 1.97) and 2.64 (95 % CI: 2.05, 3.35) respectively. An increased ratio of 6.91 (95 % CI: 3.45, 12.36), fulfilling the threshold of a prioritised safety signal, was also observed following a third dose of ChAdOx1. The aggregated OE ratios for pericarditis were increased following all doses of all the three vaccines presented (Table 4). The results are very similar to the ratios of homologous schedules (Fig. 3), except for the OE ratio of 1.23 (95 % CI: 0.45–2.69) after receipt of the fourth mRNA-1273 dose, which did not meet the threshold for a safety signal. The homologous OE ratio following a third dose of ChAdOx1 was not reported as only a small number of third doses of ChAdOx1 were given across study sites (Table1).

3.4. Sensitivity analysis

Secondary analyses were conducted to further explore GBS, ADEM, CVST, myocarditis, and pericarditis at the site-specific level. We report the aggregated OE ratios by last dose and site in the period 0–42 days after vaccination in Supplementary Tables 6–10. It was not possible to report results for all sites and study outcomes due to insufficient person-years or less than five events observed by site privacy criteria. The majority of identified safety signals following specific vaccine brand and dose combinations from the main analysis were, however, confirmed by individual sites where data were available. The supplementary analysis with person-years threshold of 1,000 and including other vaccines and doses administered within the GVDN sites, showed an increased OE ratio for some outcomes, e.g. for generalized seizures following a first dose of Gamaleya Research Institute/Sputnik vaccine (5.50, 95 % CI: 2.74, 9.84) (Supplementary Tables 11–13).

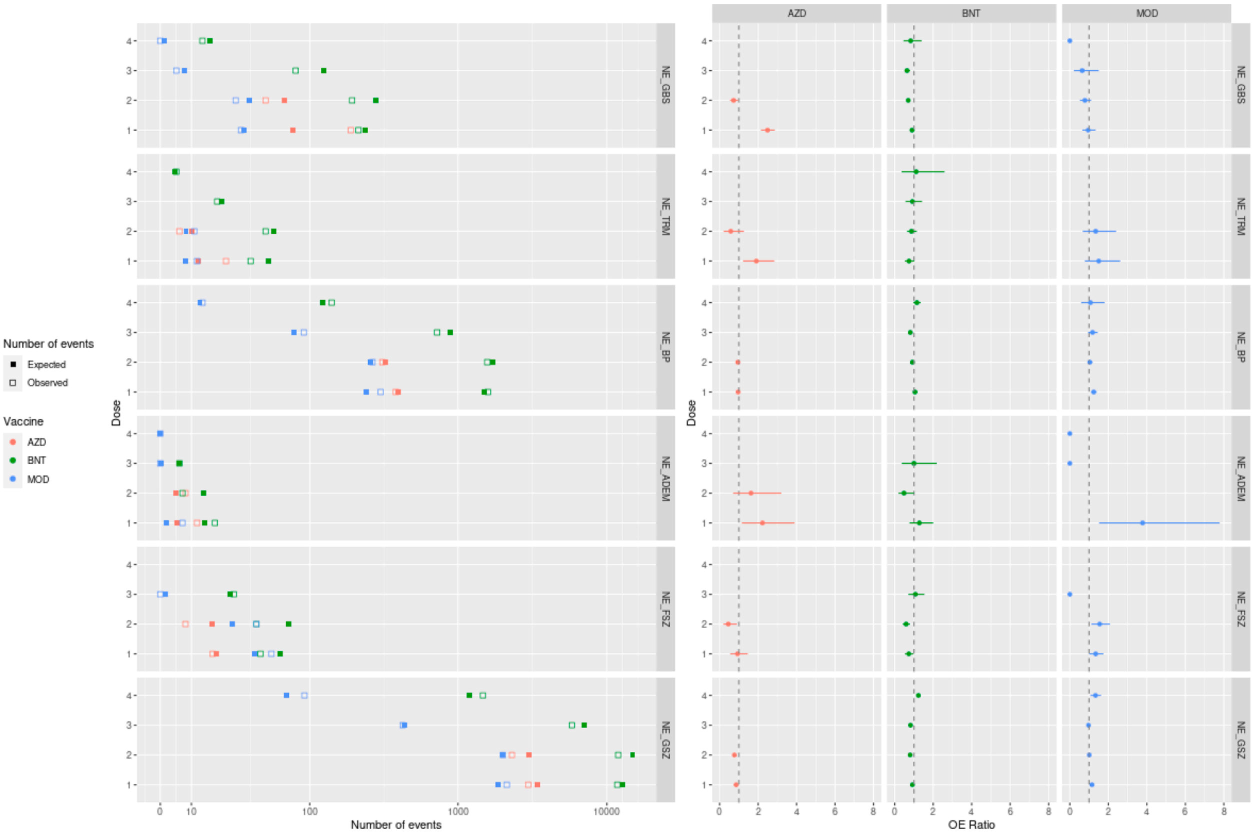


Fig. 1. Number of events and OE ratios (with 95 % confidence interval) for homologous schedules by dose 1–4, neurological conditions. AESI: GBS = Guillain-Barré syndrome, TRM = Transverse myelitis, BP = Facial (Bell's) palsy, ADEM = Acute disseminated encephalomyelitis, FSZ = Febrile seizures, GSZ = Generalised seizures. Vaccines: AZD = Oxford/Astra Zeneca/Serum Institute of India ChAdOx1, BNT = Pfizer/BioNTech (BNT162b2), MOD = Moderna (mRNA-1273).

4. Discussion

This multi-country cohort study was conducted in the unique setting of the GVDN. To date, the number of such large systematically coordinated studies across diverse geographical locations and populations is limited. However, several studies have previously assessed the risks of the identified safety signals following COVID-19 vaccination, primarily in single site settings. We investigated the association between COVID-19 vaccination and 13 AESIs comprising neurological, haematological, and cardiovascular conditions across 10 sites in eight countries including Europe, North America, South America, and Oceania. In this study including more than 99 million people vaccinated against SARS-CoV-2, the risk up to 42 days after vaccination was generally similar to the background risk for the majority of outcomes; however, a few potential safety signals were identified. We observed potential safety signals for GBS and CVST after the first dose of ChAdOx1 based on more than 12 million doses administered.

Overall, studies of the vector-based vaccines such as the ChAdOx1, have observed a higher incidence of GBS after vaccination compared with the background incidence; whereas, most studies of the mRNA vaccines, such as BNT162b2 and mRNA-1273, have not observed increases of GBS [14,15,24–27]. Atzenhoffer et al. [24] reported an elevated OE ratio > 2.0 for adenovirus-vectored COVID-19 vaccines, across countries contributing to VigiBase, an international database of adverse drug events and Patone et al. [27] reported 38 excess cases of GBS per 10 million exposed in the 1–28 days risk period following vaccination with ChAdOx1 in England. The authors did not observe an increased risk in those who received BNT162b2. In contrast, a study by Li et al. [28] showed no increased risk of GBS for ChAdOx1, while only SARS-CoV-2 infection was associated with a higher risk. The discrepancy, compared with the results of Patone et al. [27], could however be explained by a smaller sample size and different outcome measures. Overall, this evidence supports our findings of a GBS safety signal following ChAdOx1 vaccination. Although rare, this association was acknowledged by the WHO, the European Medicines Agency (EMA), and Therapeutic Goods Administration (TGA) of Australia, resulting in GBS being listed as a rare side effect following exposure to ChAdOx1 [15,29,30].

The identified increased risk of CVST following ChAdOx1 vaccination in this study is corroborated by multiple studies. An increased OE ratio was observed in a nationwide cohort study from Denmark and Norway, with increased rates of venous thromboembolic events, including CVST with an excess rate of 2.5 events per 100,000 vaccinations following ChAdOx1 [7]. Based on a variety of methodologies, other studies have also reported increased incidence of CVST after vaccination [31,32]. Ultimately, this rare but concerning safety signal led to the withdrawal of the ChAdOx1 vaccine from COVID-19 vaccine programs or implementation of age-based restrictions in multiple countries [8].

It is crucial to acknowledge the significance threshold of prioritised safety signals applied in this study (LBCI > 1.5). This threshold was selected based on expert opinion within the GVDN and at CDC, to focus on those outcomes most likely to be true signals. Some observed events, although not fulfilling this threshold, may still hold clinical importance and require further investigation. For instance, ITP with an OE ratio > 1.0 and LBCI of 1.2 following vaccination with ChAdOx1 aligns with findings reported in the literature as a potential signal. This concurrence is highlighted in a study conducted in Victoria, Australia, which observed a substantially higher than expected rate of ITP following ChAdOx1 vaccination [33].

Moreover, we observed significantly higher risks of myocarditis following the first, second and third doses of BNT162b2 and mRNA-1273 as well as pericarditis after the first and fourth dose of mRNA-

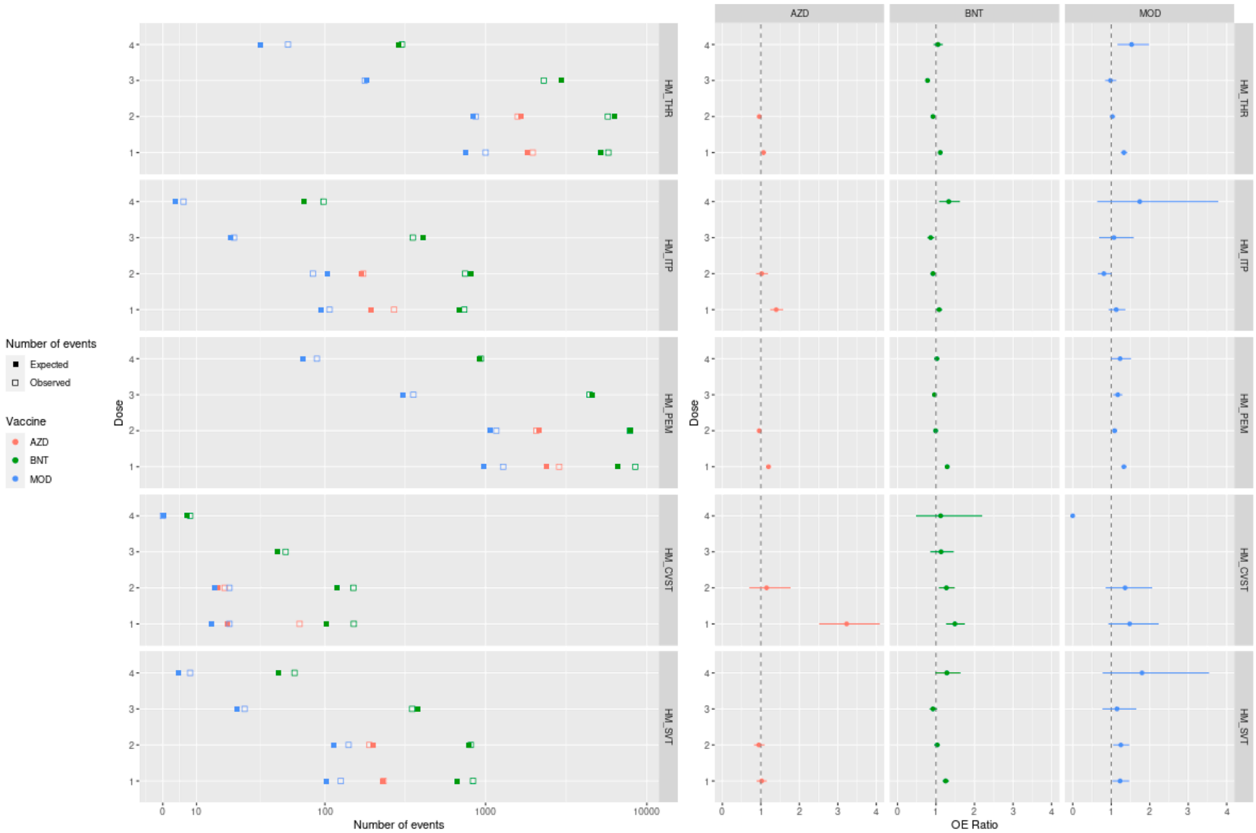


Fig. 2. Number of events and OE ratios (with 95 % confidence interval) for homologous schedules by dose 1–4, hematologic conditions. AESI: THR = Thrombocytopenia, ITP = Idiopathic thrombocytopenia, PEM = Pulmonary embolism, CVST = Cerebral venous sinus thrombosis, SVT = Splanchnic vein thrombosis. Vaccines: AZD = Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1), BNT = Pfizer/BioNTech (BNT162b2), MOD = Moderna (mRNA-1273).

1273, and third dose of ChAdOx1, in the 0–42 days risk period. The elevated rates of pericarditis following ChAdOx1 vaccination identified in this study rely on a limited number of observed counts in the meta-analysis. The wide confidence interval underscores the substantial uncertainty of characterizing pericarditis as a safety signal following ChAdOx1 vaccination. However, our study confirms findings of previously identified rare cases of myocarditis and pericarditis following first and second doses of mRNA vaccines [21–23,34]. A large cohort study of 23.1 million residents across four Nordic countries revealed an increased risk of myocarditis among young males aged 16–24 years, based on 4–7 excess events in 28 days per 100,000 vaccinees after a second dose of BNT162b2, and between 9 and 28 per 100,000 vaccinees after a second dose of mRNA-1273 [22]. Similarly, studies from British Columbia, Canada reported cases of myocarditis to be higher among those receiving a second dose compared with a third dose, and for those who received a second dose of the mRNA-1273 vaccine compared with the BNT162b2 vaccine [35,36]. Patone et al. [37] estimated extra myocarditis events to be between one and 10 per million persons in the month following vaccination, which was substantially lower than the 40 extra events per million persons observed following SARS-CoV-2 infection period. A systematic review by Alami et al. [38] concluded that mRNA vaccinated individuals were twice as likely to develop myocarditis/pericarditis compared with unvaccinated individuals, with a rate ratio of 2.05 (95 % CI 1.49–2.82). Given the evidence, WHO issued updated guidance regarding these safety signals and mRNA COVID-19 vaccination, and EMA provided updates to the Product Information for BNT162b2 and mRNA-1273 vaccines [21,23]. TGA as well as the CDC continue to monitor and review data on myocarditis and pericarditis following COVID-19 vaccination [39,40].

Another potential safety signal was identified for ADEM after the first dose of mRNA-1273 vaccine, with five more observed than expected events based on 1,035,871 person-years and 10.5 million doses administered; however, the number of cases of this rare event were small and the confidence interval wide, so results should be interpreted with caution and confirmed in future studies. Although some case reports have suggested a possible association between COVID-19 vaccination and ADEM, there was no consistent pattern in terms of vaccine or timing following vaccination, and larger epidemiological studies have not confirmed any potential association [41–44]. Moreover, case reports may report on coincidental events and do not establish association nor indicate causality, thus larger observational studies are warranted to further investigate our finding. To address this, a follow-up study is currently being undertaken within the GVDN, focusing on a demographic not included in our analysis. Based on reports of rare ADEM cases to the European Database of Suspected Adverse Drug Reaction, EMA assessed the potential association of ADEM following vaccination with ChAdOx1 [45]. Frontera et al. [46] concluded that chances of having a neurological event following acute SARS-CoV-2 infection were up to 617-fold higher than following COVID vaccination, suggesting that the benefits of vaccination substantially outweigh the risks. A safety signal for generalized seizures was identified following Gamaleya Research Institute/Sputnik vaccination, however the number of vaccinations was relatively low compared with other vaccines in this study. Further studies are warranted to explore this potential safety signal.

Conducting a cohort analysis in the unique multi-country context of the GVDN leverages a vast and diverse data pool. Aggregating data from multiple countries on more than 99 million vaccine recipients has significantly increased the sample size and the statistical power compared with many previous safety studies. This enhances the ability to detect safety signals, especially for extremely rare adverse events, as the larger sample size provides greater precision in estimating observed rates.

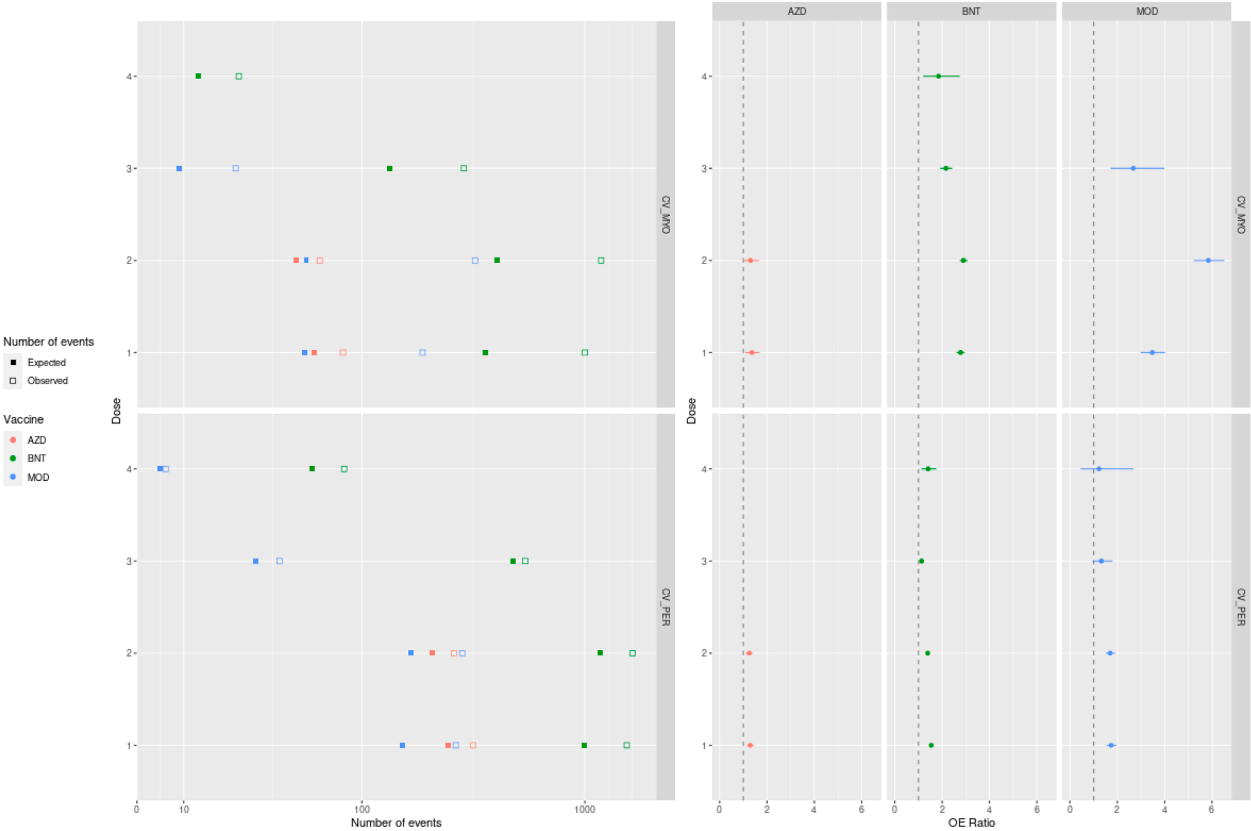


Fig. 3. Number of events and OE ratios (with 95 % confidence interval) for homologous schedules by dose 1–4, cardiovascular conditions. AESI: MYO = Myocarditis, PER = Pericarditis. Vaccines: Vaccines: AZD = Oxford/Astra Zeneca/Serum Institute of India (ChAdOx1), BNT = Pfizer/BioNTech (BNT162b2), MOD = Moderna (mRNA-1273).

Results based on data across Europe, North and South America and Oceania offer stronger external validity, enabling findings to be more generalizable to a broader range of populations and healthcare settings participating in the global COVID-19 vaccination programme. Moreover, multi-country analyses facilitate comparisons between countries with varying vaccination strategies, population demographics, and healthcare systems, yielding insights into how these factors may influence vaccine safety profiles. Data used in our analysis were drawn from multiple databases, including healthcare databases, national immunization registries, and vaccination dashboards, allowing the identification of potential safety signals from various sources.

The results from our study should, however, be interpreted considering multiple limitations. Our analyses inherently involve heterogeneity in data collection, quality, and reporting standards across countries. These differences in healthcare infrastructure and surveillance systems can introduce bias and affect the comparability of results. The participating sites across the eight countries implemented varied vaccination strategies, including vaccine types, dosing schedules, and prioritization of vaccine recipients. Moreover, the multi-country analyses are susceptible to population confounding factors, such as differences in pre-existing health conditions, genetic factors, ethnic profiles, and behavioural patterns, which was not possible to adjust for in our analysis. We consider our approach suitable for application in large datasets representing average populations. However, age- and sex-specific historic background rates that are not adjusted for factors like prior disease may not provide a suitable comparison, for example, in the early stages of a vaccination campaigns where people with co-morbidities were vaccinated prior to other population groups.

Potential underreporting across countries may have led to an underestimation of the significance of potential safety signals. It is important to recognize the potential for false negatives, especially when detecting associations with lower confidence intervals below 1.5 that maintain statistical significance. The safety signals identified in this study should be evaluated in the context of their rarity, severity, and clinical relevance. Moreover, overall risk–benefit evaluations of vaccination should take the risk associated with infection into account, as multiple studies demonstrated higher risk of developing the events under study, such as GBS, myocarditis, or ADEM, following SARS-CoV-2 infection than vaccination. Finally, the use of ICD-10 codes is subject to considerations about specificity and sensitivity, and application may vary by country.

5. Conclusion

Observed vs. expected analyses in a multi-country context of the GVDN and the GCoVS Project offers a larger and more diverse dataset, enhanced generalizability, and improved statistical power over single site or regional studies. It also presents challenges related to data heterogeneity, population confounding factors, and variations in vaccination strategies and reporting systems. The involvement of researchers and data sources from diverse regions of the world promotes inclusivity, reduces potential biases, and fosters collaboration in the pursuit of a shared public health goal. While our study confirmed previously identified rare safety signals following COVID-19 vaccination and contributed evidence on several other important outcomes, further investigation is warranted to confirm associations and assess clinical significance. This could be addressed by conducting association studies specific to individual outcomes by applying methodologies such as the self-controlled case series (SCCS) to validate the associations [6].

Disclaimer

All analyses, inferences drawn, opinions, conclusions, and statements are those of the authors and do not necessarily represent the official views of, nor an endorsement by, CDC/HHS, or the U.S. Government. For more information, please visit cdc.gov.

Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information and the Ontario Ministry of Health. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this material are based data and/or information provided by the British Columbia Ministry of Health. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Funding statement

The GCoVS project is supported by the Centers for Disease Control and Prevention (CDC) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award totalling US $10,108,491 with 100 % per cent funded by CDC/HHS.

The Ontario site contributing to this study was supported by Public Health Ontario and by the ICES, which is funded by an annual grant from the Ontario Ministry of Health. JCK is supported by a Clinician-Scientist Award from the University of Toronto Department of Family and Community Medicine.

CRediT authorship contribution statement

K. Faksova: Visualization, Writing – original draft, Writing – review & editing. **D. Walsh:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Conceptualization, Writing – review & editing, Visualization. **Y. Jiang:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing. **J. Griffin:** Conceptualization, Writing – review & editing, Methodology. **A. Phillips:** Conceptualization, Methodology, Writing – review & editing, Investigation, Validation. **A. Gentile:** Data curation, Investigation, Supervision, Validation. **J.C. Kwong:** Data curation, Supervision, Validation, Writing – review & editing, Investigation, Methodology. **K. Macartney:** Data curation, Supervision, Validation, Writing – review & editing, Investigation, Methodology. **M. Naus:** Data curation, Supervision, Validation, Investigation, Methodology. **Z. Grange:** Data curation, Supervision, Validation, Conceptualization, Investigation, Methodology. **S. Escolano:** Data curation, Supervision, Validation, Investigation, Methodology, Writing – review & editing. **G. Sepulveda:** Data curation, Formal analysis, Software, Validation. **A. Shetty:** Data curation, Validation, Investigation, Methodology. **A. Pillsbury:** Data curation, Validation, Investigation, Methodology, Writing – review & editing. **C. Sullivan:** Data curation, Validation, Investigation, Methodology, Writing – review & editing. **Z. Naveed:** Data curation, Validation, Investigation, Methodology, Writing – review & editing. **N.Z. Janjua:** Data curation, Writing – review & editing. **N. Giglio:** Data curation, Investigation, Methodology, Validation. **J. Perälä:** Data curation, Investigation, Methodology, Validation. **S. Nasreen:** Conceptualization, Data curation, Validation, Writing – review & editing. **H. Gidding:** Conceptualization, Validation, Writing – review & editing, Investigation, Methodology. **P. Hovi:** Conceptualization, Validation, Writing – review & editing, Investigation, Methodology. **T. Vo:** Conceptualization, Validation, Formal analysis, Investigation, Methodology, Writing – review & editing. **F. Cui:** Conceptualization, Investigation, Methodology, Validation. **L. Deng:** Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. **L. Cullen:** Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. **M. Artama:** Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. **H. Lu:** Data curation, Formal analysis, Software, Validation. **H.J. Clothier:** Conceptualization, Methodology, Validation, Writing – review & editing, Data curation, Formal analysis, Project administration. **K. Batty:** Conceptualization, Methodology, Project administration, Validation, Writing – review & editing. **J. Paynter:** Conceptualization, Methodology, Supervision, Data curation, Formal analysis, Writing – review & editing. **H. Petousis-Harris:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing, Project administration. **J. Buttery:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing, Project administration. **S. Black:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **A. Hviid:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jeffrey C. Kwong reports financial support was provided by Centers for Disease Control and Prevention. Naveed Z. Janjua reports financial support was provided by Centers for Disease Control and Prevention. Anders Hviid reports financial support was provided by Global Vaccine Data Network. Helen Petousis-Harris reports financial support was provided by New Zealand Ministry of Health. Steven Black reports a relationship with GSK that includes: consulting or advisory. Jeffrey C. Kwong reports a relationship with Canadian Institutes of Health Research that includes: funding grants. Jeffrey C. Kwong reports a relationship with Public Health Agency of Canada that includes: funding grants. Naveed Z. Janjua reports a relationship with AbbVie Inc that includes: consulting or advisory and speaking and lecture fees. Naveed Z. Janjua reports a relationship with Gilead Sciences Inc that includes: speaking and lecture fees. Anders Hviid reports a relationship with Independent Research Fund Denmark that includes: funding grants. Anders Hviid reports a relationship with Lundbeck Foundation that includes: funding grants. Anders Hviid reports a relationship with Novo Nordisk Foundation that includes: funding grants. Anders Hviid reports a relationship with VAC4EU that includes: consulting or advisory. Finnish Institute for Health and Welfare (THL) conducts Public-Private Partnership with vaccine manufacturers and has received research funding from Sanofi Inc. Petteri Hovi has been an investigator in these studies, but has received no personal remuneration. Helen Petousis-Harris has served on expert advisory boards and had speaking engagements for Pfizer and GSK. She has also received research funding from GSK. She has not received any personal honoraria. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Acknowledgements

The Observed vs Expected Analyses Of COVID-19 Vaccine Adverse Events of Special Interest Study Protocol was developed by the Observed vs. Expected Work Group led by Anders Hviid[a,b]. Members of the Work Group were Nelson Aguirre Duarte[c], Miia Artama[d], Karin Batty[e], Steven Black[c,f], Hannah Chisholm[c], Hazel Clothier[g,h,i], Fuqiang Cui[j], Lucy Deng[k], Lucy Cullen[l], Heather Gidding[k,m,n], Petteri Hovi[o], Yannan Jiang[c], Janine Paynter[c], Helen Petousis-Harris[c], Anastasia Phillips[k], John Sluyter[c], Thuan Vo[d,o], and Daniel Walsh[c], Eric Weintraub[p].

Work group affiliations

a. Statens Serum Institut, Denmark; b. University of Copenhagen, Denmark; c. University of Auckland, New Zealand; d. Tampere University, Finland; e. Auckland UniServices Limited at University of Auckland, New Zealand; f. University of Cincinnati and Children's Hospital, USA; g. Victorian Department of Health, Australia; h. Murdoch Childrens Research Institute, Australia; i. Centre for Health Analytics, Melbourne Children's Campus, Australia; j. Peking University, Beijing, China; k. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Australia; l. Public Health Scotland, Glasgow, Scotland, United Kingdom; m. Kolling Institute, Northern Sydney Local Health District, Australia; n. University of Sydney Northern Clinical School, Australia; o. Finnish Institute for Health and Welfare, Finland; p. Vaccine Safety Datalink, Centers for Disease Control and Prevention.

The following individuals contributed as GVDN site leads: Anders Hviid (Denmark); Angela Gentile (Argentina); Sylvie Escolano (France); Eero Poukka (Finland); Jeffrey C. Kwong (Ontario, Canada); Kristine Macartney (New South Wales, Australia); Jim Buttery (Victoria, Australia); Monika Naus (British Columbia, Canada); Zoe Grange (Scotland); and Helen Petousis-Harris (New Zealand).

The following individuals contributed as GVDN site investigators: Gonzalo Sepulveda and Aishwarya Shetty (Victoria, Australia); Alexis Pillsbury (New South Wales, Australia); Christopher Sullivan (Scotland); Naveed Zaeema (British Columbia, Canada); Norberto Giglio (Argentina); Jori Perälä (Finland); Sharifa Nasreen (Ontario, Canada); Han Lu (New Zealand).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.01.100.

References

[1] World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020 (accessed October 13, 2023).

[2] Our World in Data. Coronavirus (COVID-19) Vaccinations - Our World in Data 2023. https://ourworldindata.org/covid-vaccinations (accessed October 13, 2023).

[3] Safety Platform for Emerging Vaccines S. D2.3 Priority list of adverse events of special interest: COVID-19. Brighton Collaboration; 2020. Available from: https://zenodo.org/records/6656179#.Y-0yxuyZOnN.

[4] van der Boom MDX, van Eekeren R, van Hunsel FPAM. Observed-over-Expected analysis as additional method for pharmacovigilance signal detection in large-scaled spontaneous adverse event reporting. Pharmacoepidemiol Drug Saf 2023; 32:783–94. https://doi.org/10.1002/pds.5610.

[5] Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiol Drug Saf 2016;25: 215. https://doi.org/10.1002/PDS.3918.

[6] Li R, Stewart B, Weintraub E. Evaluating efficiency and statistical power of self-controlled case series and self-controlled risk interval designs in vaccine safety. J Biopharm Stat 2016;26:686–93. https://doi.org/10.1080/10543406.2015.1052819.

[7] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114. https://doi.org/10.1136/bmj.n1114.

[8] European Medicines Agency. Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant])-Vaxzevria (previously COVID-19 Vaccine AstraZeneca) (Other viral vaccines). 2021.

[9] Global Vaccine Data Network. Observed vs. expected analyses of COVID-19 vaccine adverse events of special interest study protocol. Version 1.4. Auckland (NZ): Global Vaccine Data Network; 2022. Available from: https://www.globalvaccinedatanetwork.org/sites/globalvaccinedatanetwork.org/files/2024-01/GVDN-observed-vs.-expected-analyses-of-COVID-19-vaccine-AESI-V1.4.pdf.

[10] Global Vaccine Data Network. Global COVID Vaccine Safety (GCoVS). Auckland (NZ): Global Vaccine Data Network; 2022 [accessed 2023 October 13]. Available from: https://www.globalvaccinedatanetwork.org/global-covid-vaccine-safety-gcovs.

[11] Global Vaccine Data Network. Auckland (NZ): Global Vaccine Data Network; 2023 [accessed 2023 October 13]. Available from: https://www.globalvaccinedatanetwork.org/.

[12] Global Vaccine Data Network. GVDN: Observed vs expected (OE) dashboard. Auckland (NZ): Global Vaccine Data Network; 2023 [updated 2023 December 8; cited 2023 December 13]. Available from: www.globalvaccinedatanetwork.org/Data-Dashboards.

[13] Phillips A, Jiang Y, Walsh D, Andrews N, Artama M, Clothier H, et al. Background rates of adverse events of special interest for COVID-19 vaccines: a multinational Global Vaccine Data Network (GVDN) analysis. Vaccine 2023;41:6227–38. https://doi.org/10.1016/J.VACCINE.2023.08.079.

[14] Hanson KE, Goddard K, Lewis N, Fireman B, Myers TR, Bakshi N, et al. Incidence of Guillain-Barré syndrome after COVID-19 vaccination in the vaccine safety datalink. JAMA Netw Open 2022;5:E228879. https://doi.org/10.1001/JAMANETWORKOPEN.2022.8879.

[15] World Health Organization. Statement of the WHO Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee on reports of Guillain-Barré Syndrome (GBS) following adenovirus vector COVID-19 vaccines n.d. https://www.who.int/news/item/26-07-2021-statement-of-the-who-gacvs-covid-19-subcommittee-on-gbs (accessed October 23, 2023).

[16] Keizer RJ, Huitema ADR, Schellens JHM, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49:493–507. https://doi.org/10.2165/11531280-000000000-00000.

[17] World Health Organization. Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield). Accessed October 23, 2023. https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield).

[18] Burn E, Li X, Kostka K, Stewart HM, Reich C, Seager S, et al. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries. Pharmacoepidemiol Drug Saf 2022;31:495–510. https://doi.org/10.1002/PDS.5419.

[19] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021;384:2092–101. https://doi.org/10.1056/NEJMOA2104840/SUPPL_FILE/NEJMOA2104840_DISCLOSURES.PDF.

[20] Hviid A, Hansen JV, Thiesson EM, Wohlfahrt J. Association of AZD1222 and BNT162b2 COVID-19 vaccination with thromboembolic and thrombocytopenic events in frontline personnel: a retrospective cohort study. Ann Intern Med 2022; 175:541–6. https://doi.org/10.7326/M21-2452.

[21] World Health Organization. COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS): updated guidance regarding myocarditis and pericarditis reported with COVID-19 mRNA vaccines. Accessed October 23, 2023. https://www.who.int/news/item/09-07-2021-gacvs-guidance-myocarditis-pericarditis-covid-19-mrna-vaccines.

[22] Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, et al. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. JAMA Cardiol 2022;7:600–12. https://doi.org/10.1001/JAMACARDIO.2022.0583.

[23] Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory committee on immunization practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–82. 10.15585/MMWR.MM7027E2.

[24] Atzenhoffer M, Auffret M, Pegat A, Masmoudi K, Khouri C, Bertin B, et al. Guillain-Barré syndrome associated with COVID-19 vaccines: a perspective from spontaneous report data. Clin Drug Investig 2022;42:581. https://doi.org/10.1007/S40261-022-01164-4.

[25] Otero-Losada M, Petrovsky N, Alami A, Crispo JA, Mattison D, Capani F, et al. Disproportionality analysis of adverse neurological and psychiatric reactions with the ChAdOx1 (Oxford-AstraZeneca) and BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines in the United Kingdom. Expert Opin Drug Saf 2023;22:343–9. https://doi.org/10.1080/14740338.2022.2120607.

[26] Walker JL, Schultze A, Tazare J, Tamborska A, Singh B, Donegan K, et al. Safety of COVID-19 vaccination and acute neurological events: a self-controlled case series in England using the OpenSAFELY platform. Vaccine 2022;40:4479–87. https://doi.org/10.1016/J.VACCINE.2022.06.010.

[27] Patone M, Handunnetthi L, Saatci D, Pan J, Katikireddi SV, Razvi S, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med 2021;27:2144. https://doi.org/10.1038/S41591-021-01556-7.

[28] Li X, Raventós B, Roel E, Pistillo A, Martinez-Hernandez E, Delmestri A, et al. Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis. BMJ 2022:376. https://doi.org/10.1136/BMJ-2021-068373.

[29] European Medicines Agency. Vaxzevria (previously COVID-19 Vaccine AstraZeneca) | European Medicines Agency. Accessed October 26, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria#product-information-section.

[30] COVID-19 vaccine weekly safety report - 09-12-2021 | Therapeutic Goods Administration (TGA). Accessed December 5, 2023. https://www.tga.gov.au/news/covid-19-vaccine-safety-reports/covid-19-vaccine-weekly-safety-report-09-12-2021#section-1298.

[31] Schulz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. Ann Neurol 2021;90: 627–39. https://doi.org/10.1002/ANA.26172.

[32] Andrews NJ, Stowe J, Ramsay ME, Miller E. Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and BNT162b2

COVID-19 vaccines: a national cohort study in England. Lancet Reg Heal Eur 2022; 13. doi: 10.1016/J.LANEPE.2021.100260.

[33] Gordon SF, Clothier HJ, Morgan H, Buttery JP, Phuong LK, Monagle P, et al. Immune thrombocytopenia following immunisation with Vaxzevria ChadOx1-S (AstraZeneca) vaccine, Victoria. Australia Vaccine 2021;39:7052–7. https://doi.org/10.1016/J.VACCINE.2021.10.030.

[34] Buchan SA, Seo CY, Johnson C, Alley S, Kwong JC, Nasreen S, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccination by vaccine product, schedule, and interdose interval among adolescents and adults in Ontario, Canada. JAMA Netw Open 2022;5:E2218505. https://doi.org/10.1001/JAMANETWORKOPEN.2022.18505.

[35] Naveed Z, Li J, Spencer M, Wilton J, Naus M, García HAV, et al. Observed versus expected rates of myocarditis after SARS-CoV-2 vaccination: a population-based cohort study. CMAJ 2022;194:1529–36. https://doi.org/10.1503/CMAJ.220676.

[36] Naveed Z, Li J, Wilton J, Spencer M, Naus M, Velásquez García HA, et al. Comparative risk of myocarditis/pericarditis following second doses of BNT162b2 and mRNA-1273 coronavirus vaccines. J Am Coll Cardiol 2022;80:1900–8. https://doi.org/10.1016/J.JACC.2022.08.799.

[37] Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2021;28:410–22. https://doi.org/10.1038/s41591-021-01630-0.

[38] Alami A, Krewski D, Farhat N, Mattison D, Wilson K, Gravel CA, et al. Risk of myocarditis and pericarditis in mRNA COVID-19-vaccinated and unvaccinated populations: a systematic review and meta-analysis. BMJ Open 2023;13:e065687. https://doi.org/10.1136/BMJOPEN-2022-065687.

[39] COVID-19 vaccine safety report - 13-07-2023 | Therapeutic Goods Administration (TGA) n.d. https://www.tga.gov.au/news/covid-19-vaccine-safety-reports/covid-19-vaccine-safety-report-13-07-2023#myocarditis-and-pericarditis-after-covid19-vaccination (accessed December 5, 2023).

[40] Myocarditis and Pericarditis After mRNA COVID-19 Vaccination | CDC n.d. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html (accessed December 5, 2023).

[41] Brock K, Reyes SC, Conner C, Gillson N, Weiss M, Elfituri O, et al. Acute disseminated encephalomyelitis (ADEM)-like illness in a pediatric patient following COVID-19 vaccination. BJR | Case Rep 2023;9. https://doi.org/10.1259/BJRCR.20220097.

[42] Nimkar SV, Yelne P, Gaidhane SA, Kumar S, Acharya S, Gemnani RR. Fatal acute disseminated encephalomyelitis post-COVID-19 vaccination: a rare case report. Cureus 2022;14. https://doi.org/10.7759/CUREUS.31810.

[43] Permezel F, Borojevic B, Lau S, de Boer HH. Acute disseminated encephalomyelitis (ADEM) following recent Oxford/AstraZeneca COVID-19 vaccination. Forensic Sci Med Pathol 2022;18:74–9. https://doi.org/10.1007/S12024-021-00440-7.

[44] Khan S, Khan S, Waqar Z, Mobeen H, Khan N, Hassan M. Post Moderna Vaccine associated acute disseminated encephalomyelitis (ADEM) - a case report. Pak J Neurol Sci 2022;17. 10.56310/PJNS.V17I01.186.

[45] European Medicines Agency. *COVID-19 Vaccine Safety Update.*; 2021. https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-18-june-2021_en.pdf.

[46] Frontera JA, Tamborska AA, Doheim MF, Garcia-Azorin D, Gezegen H, Guekht A, et al. Neurological events reported after COVID-19 vaccines: an analysis of vaccine adverse event reporting system. Ann Neurol 2022;91:756–71. https://doi.org/10.1002/ANA.26339.